



4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 211

[Docket No. FDA-1997-N-0518] (formerly 97N-0300)

Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; Revision of Certain Labeling Controls

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the packaging and labeling control provisions of the current good manufacturing practice (CGMP) regulations for human and veterinary drug products by limiting the application of special control procedures for the use of cut labeling to immediate container labels, individual unit cartons, or multiunit cartons containing immediate containers that are not packaged in individual unit cartons. FDA is also permitting the use of any automated technique, including differentiation by labeling size and shape, that physically prevents incorrect labeling from being processed by labeling and packaging equipment when cut labeling is used. This action is intended to protect consumers from labeling errors more likely to cause adverse health consequences, while eliminating the regulatory burden of applying the rule to labeling unlikely to reach or adversely affect consumers. This action is also intended to permit manufacturers to use a broader range of error prevention and labeling control techniques than permitted by current CGMPs.

DATES: This final rule is effective on March 20, 2013, except for the amendment adding [§ 211.122\(g\)\(4\)](#), which is effective [INSERT DATE 30 DAYS AFTER DATE OF

PUBLICATION IN THE FEDERAL REGISTER].

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SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of July 29, 1997 (62 FR 40489) (the proposed rule), FDA proposed to amend the packaging and labeling control provisions of the CGMP regulations for human and veterinary drug products by limiting the application of special control procedures for the use of cut labeling to immediate container labels, individual unit cartons, or multiunit cartons containing immediate containers that are not packaged in individual unit cartons, and to permit the use of any automated technique, including differentiation by labeling size and shape, that physically prevents incorrect labeling from being processed by labeling and packaging equipment when cut labeling--single labels for individual drug products that are "cut" from a sheet or roll of labels--is used.

Persistent problems with drug product mislabeling and subsequent recalls led FDA in 1987 and in 1990 to review labeling procedures and product recalls. The review identified gang-printed and cut labeling as a leading cause of labeling mixups. Gang-printed labeling is defined in § 210.3(b)(22) (21 CFR 210.3(b)(22)) as labeling derived from a sheet of material on which more than one item of labeling is printed. Each sheet includes labeling for a variety of products and, because of this, labeling for individual drug products must be separated from the labeling for other products. When labels are gang-printed, the labels for different drug products or different strengths for the same drug product are processed together, making them especially

susceptible to mixups. Similarly, cut labeling is commonly placed in separate stacks before being transported to packaging and labeling lines for application to appropriate products. FDA found that stacks of labeling of similar size, shape, and color could easily be intermixed and, if the printer or manufacturer did not detect the error, incorrect labeling could be applied and a mislabeled drug product distributed. To reduce the frequency and likelihood of such mislabeling, FDA, in the Federal Register of August 3, 1993 (58 FR 41348), amended the packaging and labeling control provisions of the CGMP regulations in part 211 (21 CFR part 211) to provide specific conditions for the use of all gang-printed and cut labeling. Under § 211.122(f), use of gang-printed labeling for different drug products, or different strengths or net contents of the same product, is prohibited unless the labeling from gang-printed sheets is adequately differentiated by size, shape, or color. Under § 211.122(g), packaging and labeling operations must use one of three special control features if cut labeling is used: (1) Packaging and labeling lines must be dedicated to each different strength of each different drug product; (2) appropriate electronic or electromechanical equipment must be used to conduct a 100 percent examination for correct labeling during or after completion of finishing operations; or (3) where labeling is hand-applied, use of visual inspection to conduct a 100 percent examination for correct labeling during or after completion of finishing operations must be performed by one person and independently verified by a second person.

To further limit the potential for mislabeling, FDA also required written procedures for the identification and handling of filled drug product containers not immediately labeled (§ 211.130(b)). FDA also amended § 211.125(c) to exempt manufacturers that use automated 100 percent examination for correct labeling from the label reconciliation requirements. FDA also defined gang-printed labeling at § 210.3(b)(22). The final rule applied to all types of

labeling, including product inserts, multiunit containers packaged in individual containers, and shipping containers.

In May 1994, FDA received two citizen petitions from several trade associations requesting, among other things, that FDA consider additional comments on the application of § 211.122(g) to items of labeling other than the immediate container label, and requesting additional time to obtain, install, or validate equipment necessary to comply with the August 3, 1993 final rule. In response to these requests, FDA extended the compliance date to August 3, 1995, for § 211.122(g) as it applies to labeling other than immediate container labels, and opened the administrative record for comments on the scope of § 211.122(g). All other provisions of the August 3, 1993, final rule became effective on August 3, 1994. To adequately assess comments received during the extended comment period and provide industry additional time to comply with the regulation, FDA published several notices extending the compliance date for § 211.122(g), as it applies to labeling other than immediate container labels, to August 2, 1996, to August 1, 1997, and, in the July 29, 1997, Federal Register (62 FR 40447), until the effective date of this final rule.

FDA evaluated the comments received during the extended comment period, met with industry representatives, reviewed recall data to determine the danger to consumers from errors in different types of drug product labeling, and surveyed packaging and labeling control technology. On July 29, 1997, FDA issued a proposed rule to narrow the scope of § 211.122(g) and to expand the permissible control procedures. This rule finalizes the July 29, 1997, proposed rule. As described in more detail in section II of this document, the final rule adopts the proposed codified without change.

II. Description of the Final Rule

A. Scope of § 211.122

The first sentence of current states: “If cut labeling is used, packaging and labeling operations shall include one of the following special control procedures.” The final rule amends the first sentence of § 211.122(g) to state: “If cut labeling is used for immediate container labels, individual unit cartons, or multiunit cartons containing immediate containers that are not packaged in individual unit cartons, packaging and labeling operations shall include one of the following special control procedures.” Thus, instead of applying to all types of labeling as required in the August 3, 1993, final rule, the control procedures specified in revised § 211.122(g) apply only to cut labeling used for immediate container labels, individual unit cartons, or multiunit cartons containing immediate containers that are not packaged in individual unit cartons. This amendment is intended to protect consumers from labeling errors that are more likely to cause adverse health consequences, while eliminating the regulatory burden of applying the rule to labeling unlikely to reach or adversely affect consumers. As explained in the proposed rule, the immediate container label is most likely to be read by consumers. The individual unit carton labeling is the outermost container in which a drug product is commonly marketed at retail, and many consumers read this labeling when deciding whether to purchase a product. When using multiunit cartons containing immediate containers that are not packaged in individual unit cartons (for example, sterile dosage forms in tray packs in which immediate containers lack unit cartons), consumers and health professionals are more likely to rely on labeling on the outer multiunit container than to examine the labeling on the individual drug product immediate containers.

B. Special Control Procedures

Currently, there are three control procedures delineated in § 211.122(g)(1) through (g)(3): (1) Dedication of labeling and packaging lines to each different strength of each different drug product; (2) use of appropriate electronic or electromechanical equipment to conduct a 100 percent examination for correct labeling during or after completion of finishing operations; or (3) use of visual inspection to conduct a 100 percent examination for correct labeling during or after completion of finishing operations for hand-applied labeling. The visual inspection must be performed by one person and independently verified by a second person. The final rule amends § 211.122(g) to add a fourth alternative special control procedure for packaging and labeling operations when cut labeling is used that provides for more flexibility in determining adequate controls. The fourth control, added at § 211.122(g)(4), states: “Use of any automated technique, including differentiation by labeling size and shape, that physically prevents incorrect labeling from being processed by labeling and packaging equipment.” As noted in the proposed rule (62 FR 40489 at 40491), this additional control procedure is being added because FDA believes that this will provide manufacturers with the widest possible latitude in selecting appropriate labeling control technologies. It will permit the use of a number of automated techniques that will physically prevent incorrect labeling from being processed by packaging and labeling equipment. A labeling control method using size and shape as part of an automated technique that prevents incorrect labeling from being processed by labeling and packaging lines provides equivalent labeling control protection, through prevention, as do the other special control procedures through surveillance or dedication of labeling and packaging lines. An acceptable automated technique will allow labeling and packaging operations to operate only if correct labeling unique to a given product (for example, a specific size) is used.

III. Responses to Comments on the Proposed Rule

FDA received three comments on the proposed rule which raised a limited number of issues. The specific issues raised by the commenters are described in this section III.

(Comment 1) One comment said that the final rule should permit all effective means of label control, whether they involve automated systems or nonautomated systems. The comment said that FDA has indicated that both automated and nonautomated systems of label control are equally effective in preventing label mixups. The comment cited the June 23, 1989, proposed rule and the August 3, 1993, final rule, and noted that FDA said that three label control practices were not involved in any of the recalls attributed to label mixups (i.e., the use of labels differentiated by size, shape, or color; the use of dedicated packaging lines; and the use of electronic label verification systems that validate the labeling of each product during finishing operations (100 percent label inspection)). The comment said that these label control practices include both automated (the use of electronic label verification systems that validate the labeling of each product during finishing operations) and nonautomated (use of labels differentiated by size, shape, or color and the use of dedicated packaging lines) methods.

The comment also said that industry's experiences with certain electronic and electromechanical control systems have shown inconsistent results, and 50-60 percent of the electronic systems that were installed during the recent past (the comment was submitted in 1997) could not be used because of lack of reliability against the zero-defect standard. The comment said that some automated systems are not robust enough to identify "bad" labels 100 percent of the time, at certain line speeds and under certain conditions, and the systems erred with unacceptable levels of false positives (that is, flagging "good" labels as "bad").

The comment said the special control procedures under proposed § 211.122(g) should be modified to allow companies to document a system of control that best fits the unique abilities of

each particular company, without requiring any one particular control system (for example, electronic or electromechanical controls) to be used across the entire industry. The comment said this approach would allow the implementation of technology appropriate for the individual plants involved.

The comment noted that many companies currently use multiple layers of control in their labeling operations that have yielded very robust systems of total control, and they should not be required to add another special layer of control that may not improve their total system. The comment stated that FDA should permit additional automated and nonautomated methods of control for items of labeling within the scope of § 211.122(g). Differentiation by size, shape, or color or by any other effective, validated means should be permitted, whether automated or not. The comment described other types of layers of control that should be permitted, including labeling design to minimize mixups, using labeling suppliers that have excellent internal control, using label control rooms, proper purging of labeling lines, using computerized material requirements planning systems, online checks of operations, and reconciliation of labeling.

Another comment said that the proposed rule would limit industry's choice of control measures, and too great an emphasis was placed on "high tech" electronic verification systems. The comment stated that traditional methods of label control have proven to be just as effective. The comment said that industry is largely operating using traditional label control measures along with some high tech electronic verification systems as part of an overall system of label control. These traditional systems consist of multilevel control measures that work together to ensure that label mixups are avoided. The comment said that the use of electronic systems alone will not provide this level of assurance, because electronic systems are not 100 percent effective and often give false alarms in labeling operations that can lead to operator complacency and/or

inefficient line operation. The comment expressed doubt that the use of electronic verification systems would improve systems currently in place at its company. The comment recommended other control measures as part of an overall system for label control that should be considered by FDA, including: (1) An ongoing program to assess the label supplier's operations and controls; (2) labeling designed to avoid mixups such as differentiation by size, shape, and color;(3) procedures addressing art/label approval; (4) a multilevel control system that incorporates personnel training, label inspection, line clearance, and other control procedures designed to avoid mixups; and (5) a validation of such systems that gives assurance that label controls are acceptable.

(Response) First, the Agency believes that it is important to emphasize that one of the special controls listed in § 211.122(g) must be used only when cut labeling is used for the types of labeling described in § 211.122(g). Manufacturers have significant additional flexibility to use different labeling controls for other types of labeling.

When cut labeling is used for the identified types of labeling, at least one of the special controls in § 211.122(g) must be used. The final rule permits the choice of a special control from one of four options specified in § 211.122(g)(1) through (g)(4). Two are nonautomated controls: dedication of lines (paragraph (g)(1)) and visual inspection for hand applied labels (paragraph (g)(3)). Two are automated controls: Electronic or electromechanical examination to conduct a 100-percent examination for correct labeling during or after completion of finishing operations (paragraph (g)(2)), and use of any automated technique that physically prevents incorrect labeling from being processed by labeling and packaging equipment (paragraph (g)(4)). This provides industry with a number of options, including manual, electronic, electromechanical, and automated systems. It also permits broad discretion to industry to select appropriate electronic or

automated systems for this purpose, and to “layer” different controls, if desired, as long as at least one of the options listed in paragraph (g) is used as one of the layers.

However, FDA disagrees that additional nonautomated special controls, in addition to dedicated lines or visual inspection, should be added to paragraph (g). As we noted in the proposed rule (62 FR 40489 at 40491), nonautomated (i.e., manual) differentiation of size and shape as a labeling control does not provide adequate protection from labeling mixups when cut labeling is used. It is the increased opportunity for human error afforded by the process of cutting, sorting, and subsequent handling of different items of labeling that has caused labeling mixups and recalls. One of the goals of this rulemaking is to reduce the likelihood for such human error through the increased use of automated labeling control systems and through the elimination of manual label differentiation by size and shape. In addition, in response to the commenter’s concern that electronic systems are not sufficiently reliable, we believe that development and use of advanced code scanning equipment has made many current electronic verification systems accurate and reliable. For example, all prescription drug products (with limited exceptions), biological products, and certain over-the-counter (OTC) drug products are now required by 21 CFR 201.25 to bear on the label a bar code containing, at a minimum, the drug’s NDC (National Drug Code). Electronic systems can use these codes to scan the labels as part of the label controls. These and other advanced scanning techniques have made current electronic systems reliable to the 100 percent standard.

If cut labeling is used, the choice of one of the four special control procedures listed above should allow manufacturers to document a system of control that best fits the unique abilities of each particular manufacturer without requiring any one particular control system to be used. The final rule permits manufacturers considerable latitude under § 211.122(g)(1)

through (g)(4) in establishing control procedures over cut labeling, and is sufficiently flexible to permit technological innovation in automated labeling inspection systems. For example, under the final rule, a labeling control method designed by an individual manufacturer could incorporate electronic or electromechanical equipment or the use of a visual inspection to conduct a 100 percent examination for correct labeling. Moreover, manufacturers are free to use one of the specifically enumerated special controls in § 211.122(g) in combination with any other special or general labeling controls. The rule merely establishes that, at a minimum, one of the four enumerated special controls must be used when the identified types of cut labeling are used. Accordingly, many of the alternative special and general controls discussed by the commenters could also be used in conjunction with one of the enumerated special controls.

The comments suggest that this rule will mandate that manufacturers who currently have effective label control systems but are not currently using one of the controls enumerated in § 211.122 (g)(1) through (g)(4) must change their system to include one of the four special controls. FDA points out that this would only be true for situations where cut labeling is currently being used for those labels subject to the enforcement discretion period (labels other than immediate container labels) if the manufacturer is not currently voluntarily using one of the enumerated special controls. Processes using cut labeling for immediate containers labels (the bulk of the labels covered by this change) were not subject to enforcement discretion and would already be required to use one of the three special controls in current § 211.122 (g)(1) through (g)(3). The only change made by this rule for those labeling processes would be the addition of a new option to meet the requirement of subsection (g). Those lines would not be required to make any change by this final rule.

(Comment 2) One comment said that the controls for cut labeling used for multiunit

cartons containing immediate containers that are not packaged in individual unit cartons (§ 211.122(g)) should not apply to OTC drug product shelf-packs. The comment explained that OTC drug products are sometimes packaged in what could be called multiunit cartons containing immediate containers that are not packaged in individual unit cartons. These are often called "shelf-packs" or "trays." The comment gave the following examples: antacid tablets packaged in individual rolls and placed in a tray near the checkout of a drugstore or supermarket; bottles of sunscreen products displayed in an end-unit in a store for convenience and added display space; and analgesic powders in printed envelopes placed in a tray to keep them upright on the store shelf. The comment noted that for these products the immediate containers are not packaged in individual unit cartons. However, complete labeling is on the individual packages, and neither consumers nor health professionals rely on the information on the tray or end-unit to purchase or use the product. The comment said that the proposed rule could be interpreted to apply to OTC shelf-packs, trays, or end units, but that special control procedures are not needed for these products because their labeling is not relied on to purchase the products. In addition, because the labeling on the shelf pack, tray, or end unit itself does not accompany the product to its point of use, it is not relied on by the consumer to use the product. Therefore, the comment said, no significant additional protection to the public health and safety would result from special control procedures for these products. The comment recommended that proposed § 211.122(g) be revised to read: "* * * multiunit cartons containing immediate containers of prescription drugs that are not packaged in individual unit cartons* * * ."

(Response) FDA does not agree that the final rule should specifically exclude OTC shelf-packs. First, FDA disagrees with the assertion that consumers and health professionals do not rely on the information on the tray or end-unit to purchase or use the product. Although

mislabeling of immediate containers poses the most obvious threat to public health and safety, a considerable danger is also posed by errors in the labeling that influences consumer selection of the product at the time of purchase. Indeed, we believe that, in the context of shelf-packs, these requirements are more important for OTC drugs for which there is not necessarily a health care professional involved to help ensure proper product selection. FDA does not agree that the rule would significantly affect the use of shelf-packs because shelf-packs rely on other packaging and labeling operations and infrequently use cut labeling. To the extent that OTC shelf-packs do use cut labeling, the special control procedures allow manufacturers considerable latitude in establishing appropriate controls.

(Comment 3) One comment said the rule should not apply to drug products in preprinted immediate containers such as tubes, vials, cans, bottles, pouches, and blister packages. The comment requested that the final rule be revised to specifically exclude preprinted immediate containers.

(Response) FDA agrees that the rule does not apply to drug products in preprinted immediate containers because the likelihood of labeling mixups appears to be remote and because preprinted drug product containers are still subject to existing general labeling controls to prevent mixups. Preprinted immediate containers include tubes, vials, cans, bottles, pouches, and blister packages where the labeling is directly “inked” into the package. FDA does not agree that it is necessary to amend § 211.122 to expressly exclude drug products in preprinted immediate containers because, as adopted in this final rule, § 211.122 does not apply to preprinted containers.

(Comment 4) One comment requested that the rule be finalized only as currently applied to immediate container labels in § 211.122(g) and not expanded to individual unit cartons or

multiunit cartons containing immediate containers that are not packaged in individual unit cartons.

(Response) As explained earlier in this preamble, the control procedures specified in § 211.122(g) apply to cut labeling used for immediate container labels, individual unit cartons, or multiunit cartons containing immediate containers that are not packaged in individual unit cartons. This is intended to protect consumers from labeling errors that are more likely to cause adverse health consequences, while eliminating the regulatory burden of applying the rule to labeling unlikely to reach or adversely affect consumers. The immediate container label is most likely to be read by consumers. The individual unit carton labeling is the outermost container in which a drug product is commonly marketed at retail, and many consumers read this labeling when deciding whether to purchase a product. When using multiunit cartons containing immediate containers that are not packaged in individual unit cartons (for example, sterile dosage forms in tray packs in which immediate containers lack unit cartons), consumers and health professionals are likely to rely both on labeling on the outer multiunit container as well as the labeling on the individual drug product immediate containers.

(Comment 5) One comment questioned the use of the term "gang-printed materials" in the following paragraph of the proposed rule: "FDA notes, however, that nonautomated (i.e., manual) differentiation of size and shape as a labeling control does not provide adequate protection from labeling mixups. It is the increased opportunity for human error afforded by the process of cutting, sorting, and subsequent handling of different items of labeling from gang-printed materials that has caused labeling mixups and recalls. One of the goals of this proposed rulemaking is to reduce the likelihood for such human error through the use of automated labeling control systems" (62 FR 40489 at 40491 and 40492).

The comment said that this paragraph appears to equate cut labeling with gang-printing. The comment noted that gang-printing is prohibited under § 211.122(f): "Use of gang-printed labeling for different drug products, or different strengths or net contents of the same product, is prohibited unless the labeling from gang-printed sheets is adequately differentiated by size, shape, or color." In addition, gang-printed labeling is defined in § 210.3(b)(22) as "labeling derived from a sheet of material on which more than one item of labeling is printed." The comment noted that the printing of repetitions of the same item of labeling on the same sheet results in cut labeling, as the individual repetitions of the item are cut from the sheet for use. The comment said that this is not gang-printing and does not present the same opportunity "for human error afforded by the process of cutting, sorting, and subsequent handling of different items of labeling" as does gang-printing, because the labeling is all identical.

(Response) FDA acknowledges that the distinction between "gang-printed labeling" and "cut labeling" in the July 29, 1997, proposed rule (62 FR 40490) may have caused confusion among some readers. Gang-printed labeling, as explained earlier in this preamble, is defined in § 210.3(b)(22) (21 CFR 210.3(b)(22)) as labeling derived from a sheet of material on which more than one item of labeling is printed. For example, a sheet of material that contains labeling for different strengths of a drug product is considered to be gang-printed. In contrast, cut labeling, as described in the August 3, 1993, final rule (58 FR at 41350), refers to items of labeling that have been detached or "cut" from printed stock material. This stock material may or may not be gang-printed; it may contain labeling for different drug products or different strengths of the same drug product or it may contain identical labeling for the same drug product. The printing method of the stock material has no bearing on whether labeling is considered to be cut labeling. The defining feature of cut labeling is simply that it is "cut." After being cut, such

labeling is commonly sorted by type or strength of drug product (if it is not identical), placed into separate, corresponding stacks, and then transported to the packaging and labeling lines for application to the appropriate product. Cut labeling is problematic because the items, when cut and placed into individual stacks for application to different drug products, are easily mixed up. FDA found that stacks of labeling of similar size, shape, and color could easily be intermixed and, if the manufacturer did not detect the error, incorrect labeling could be applied and a mislabeled drug product distributed.

(Comment 6) One comment said that § 211.122(g)(3) should be revised to include the sentence: "Such a 100 percent examination must be conducted by one person and independently verified by a second person." The comment said by omitting this phrase the public might be led to the presumption that the "verification by a second person" is no longer required.

(Response) FDA notes that it did not propose to amend § 211.122(g)(3), nor is that section being amended by this final rule. Moreover, because the first sentence of § 211.122(g)(3) already states that "a 100-percent examination" for correct labeling is required, repeating the phrase "100-percent" in the second sentence of paragraph (3), as proposed by the commenter, would be redundant. Therefore, the final rule does not adopt the change suggested by the commenter.

(Comment 7) One comment said that the proposed compliance date of 6 months after publication of the final rule should be extended to 1 year to adequately implement any new controls.

(Response) As requested by the comment, we are providing an effective date of 1 year from the date of publication of this final rule as it applies to labels that had not previously been covered by this regulation. The application of § 211.122(g) to labeling other than labeling used

for immediate container labels has been stayed since August 3, 1994. Although it lifts the stay, the final rule also narrows the applicability of § 211.122(g) so that, in addition to immediate container labeling, the only other labeling that is subject to final § 211.122(g) is cut labeling used for individual unit cartons, or multiunit cartons containing immediate containers that are not packaged in individual unit cartons. We believe 1 year will be sufficient to permit companies to adopt an appropriate control from § 211.122(g)(1) through (g)(4) for those limited additional categories of cut labeling.

The shorter implementation period applicable to cut labeling used for immediate container labels (which make up the majority of cut labeling used) reflects the fact that sections 211.122(g)(1) through (g)(3) as they apply to such labels have been effective since August 3, 1994. As to those labels, this final rule merely adds an additional control option for the appropriate use of cut labeling (i.e., § 211.122(g)(4)). Accordingly, as to those labels, we are making this rule effective 30 days after its publication in the Federal Register. If they wish, labelers may continue to use one of the appropriate controls listed in § 211.122(g)(1) through (g)(3) that have been applicable to those labels since 1994. Adoption of the additional control option in § 211.122(g)(4) added by this final rule is purely voluntary but, since the regulation provides an alternative method of compliance, there is no reason to delay its applicability beyond the statutory 30-day period.

IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is

necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Agency believes that this final rule is not a significant regulatory action under Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this rule reduces the scope of the 1993 final rule and provides manufacturers greater flexibility to meet regulatory requirements, the Agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is \$136 million, using the most current (2010) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

The purpose of this final rule is to protect consumers from those labeling errors that are more likely to cause adverse health consequences, while eliminating the regulatory burden of applying the rule to labeling unlikely to reach or adversely affect consumers. This rule amends the 1993 final rule by limiting the scope to cut labeling for immediate container labels, individual unit cartons, and multiunit cartons containing immediate containers that are not packaged in individual unit cartons. This rule also increases flexibility for firms selecting

special labeling control procedures by adding a provision for the use of any automated technique, including differentiation by size and shape, that physically prevents incorrect labeling from being processed by labeling and packaging equipment. Therefore, this rule is expected to have a positive economic impact on drug manufacturers that would otherwise be subject to the more stringent requirements under current regulations.

V. Paperwork Reduction Act of 1995

This final rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VI. Environmental Impact

The Agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 21 CFR Part 211

Drugs, Labeling, Laboratories, Packaging and containers, Prescription drugs, Reporting and record keeping requirements, Warehouses.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 211 is amended as follows:

PART 211--CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

1. The authority citation for 21 CFR part 211 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 360b, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

2. Section 211.122 is amended by revising the introductory text of paragraph (g) and by adding paragraph (g)(4) to read as follows:

§ 211.122 Materials examination and usage criteria.

* * * * *

(g) If cut labeling is used for immediate container labels, individual unit cartons, or multiunit cartons containing immediate containers that are not packaged in individual unit cartons, packaging and labeling operations shall include one of the following special control procedures:

* * * * *

(4) Use of any automated technique, including differentiation by labeling size and shape, that physically prevents incorrect labeling from being processed by labeling and packaging equipment.

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Dated: March 13, 2012.

Leslie Kux,

Acting Assistant Commissioner for Policy.

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